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Short communication

Use of oxcarbazepine for treatment of refractory status epilepticus

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ABSTRACT

Purpose: Oxcarbazepine (OXC) is an effective anticonvulsant used for treatment of partial and secondarily generalized seizures. However, there is almost no data regarding its effectiveness and tolerability when used for treatment of status epilepticus (SE).
Methods: We retrospectively identified all patients who received OXC for treatment of SE in our hospital between July 2008 and December 2010 in our hospital and analyzed all available data.
Results: We identified 13 patients (median age 79 years) who were treated with OXC for refractory SE after failure of first- and second-line therapy in our institution. In the majority of patients, etiology was remote symptomatic (10/13), and semiology was nonconvulsive (10/13). OXC was initiated as third or later agent in almost all patients after median latency of 81 h with a median maximum daily dose of 1800 mg. OXC was the last drug before SE cessation in 8/13 patients. Relevant hyponatriemia <125 mmol/l was seen in 3 patients.
Conclusion: OXC may be an effective alternative in refractory SE, but patients need to be monitored closely for hyponatriemia.
Practice implications: OXC could be used for refractory SE under close electrolyte monitoring when standard agents fail or are unsuitable.

1. Introduction

Status epilepticus (SE) is a frequent neurological emergency that requires immediate treatment. Initial treatment consists in administration of intravenous or intramuscular benzodiazepines followed by intravenous anticonvulsant drugs such as phenytoin, valproate or levetiracetam. SE that does not cease after adequate doses of benzodiazepines and at least one intravenous anticonvulsant is labeled refractory SE. Evidence for treatment of refractory SE is scarce and mainly consists of small prospective or retrospective series. In clinical practice, patients either receive one of the other available intravenous anticonvulsants, or are put into therapeutic coma, or both. If this approach fails, one of the rescue strategies is to introduce one of the oral anticonvulsants by nasogastric tube. Topiramate (TPM)[1,2] and pregabalin (PGB)[3,4] have been used in this situation with some degree of success.

Oxcarbazepine (OXC) has been developed as follow-up compound of carbamazepine (CBZ) to avoid some of the relevant disadvantages of CBZ by using a non-oxidative metabolization pathway in contrast to the cytochrome P450-mediated metabolism of CBZ.[5] OXC has been shown to be similarly effective as CBZ for treatment of partial epilepsies.[6] Oxcarbazepine is licensed for treatment of partial and generalized seizures both as add-on and as monotherapy and thus can be maintained in SE patients even when they are discharged into outpatient setting. Therefore, it is a potentially valuable candidate for use in refractory SE.

However, as of yet, there are only scarce reports about the use OXC for treatment of SE. With this study, we intended to document our experiences with this substance in patients admitted for SE.

2. Methods

Details of patient identification and data collection can be found in.[7] In summary, we retrospectively identified all patients treated for SE in our hospital between July 2008 and December 2010. Only the first admission of a patient during this time period was analyzed. For this case series, we searched for all patients who received oxcarbazepine, carbamazepine or eslicarbazepine during the course of SE treatment.

The hospital charts were reviewed for sociodemographic data, etiology, semiology, onset of SE, and discharge. In our hospital, a standardized SE documentation form is introduced to the patient's chart at the time admission. In this simple document, the treating physician enters the drugs applied, their effect on the seizure activity, and all adverse phenomena the physician considers as most likely treatment-related. All original imaging data and EEG data were reviewed by at least one of the authors. The patients underwent neurological examination and cranial imaging (CT or

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MRI) at admission. Comorbidity and clinical outcome was assessed retrospectively based on admission and discharge documentation. We used the modified Rankin Scale (mRS), a rating scale regarding the patient's disabilities ranging from 0 (no symptoms) to 5 (bedridden, requires constant attention) respectively 6 (death). SE semiology was defined as 'generalized convulsive', 'loss of consciousness without major motor symptoms', 'aphasic/dyscognitive', 'simple motor' and 'other simple partial' (e.g. aura). SE starting with generalized convulsions was always regarded as generalized convulsive. A drug was considered as successful for treatment of SE when no further anticonvulsants were administered until cessation of SE. Time of cessation of SE was defined by the time when the seizure symptoms ceased and the patient returned to his baseline, or – if in doubt – by the time of the first EEG showing cessation of the electroencephalographic signs of SE. Equivalent doses of benzodiazepines were calculated according to established pharmacologic tables[8,9]: 10 mg diazepam = 1 mg lorazepam = 0.5 mg clonazepam = 7.5 mg midazolam.

Statistical analysis was performed using OPENSTAT (http://statpages.org, Version June 2010). Ranked variables were described using mean and standard deviation, or median/quartiles when normal distribution could not be assumed. For univariate analysis of categorical data, chi-square test and Fisher's exact test (2×2 tables) were used. Interval-scaled or ordinal-scaled data were analyzed with the Mann–Whitney-*U*-test (comparison of two groups), or the Kruskal–Wallis test (comparison of three or more groups).

3. Results

Fourteen patients were identified who had received oxcarbazepine (13 patients) and carbamazepine (1 patient) for treatment of status epilepticus. To allow for consistent analysis of the data, we excluded the patient with carbamazepine from further analysis and focussed on the oxcarbazepine patients only.

The patients (9 men/4 women) had a median age of 79 years. Etiology was remote symptomatic in 10, with pre-existing epilepsy in 7 of them. The other patients had an acute symptomatic cause for the SE. SE semiology was generalized convulsive in 2, simple motor in 1, aphasic or dyscognitive in 4, and loss of consciousness only in 6 patients. All patients had clear lateralization of the ictal discharges in their EEG. In two patients mRS was 0 or 1 before SE onset, in all other patients mRS before onset was 3 or 4.

Treatment of SE started after a median latency of 1.1 h. Five patients received the first treatment within 10–30 min after seizure onset. Oxcarbazepine was used in all but one patient in refractory SE, i.e. after failure of benzodiazepines and at least one intravenous anticonvulsant in adequate dose (see Table 1). It was used as third agent in one patient, as fourth agent in 3 patients, as fifth agent in 4 patients, and as sixth or later agent in the remaining 4 patients. The median latency from SE onset to the first administration of OXC was 81 h, ranging from 22 h to 621 h. The median first dose was 600 mg, the median max. Daily dose was 1800 mg. In 8 (61.5%) of the patients, OXC was the last drug before SE cessation. SE ceased within 6 h after first administration in 2 patients, and after more than 24 h (median: 144 h) in the other patients. In three patients, OXC-related side effects (hyponatriemia in all cases) were seen. Minimum sodium serum levels in those patients were 112 mmol/l, 121 mmol/l and 125 mmol/l respectively. In the first two instances, the patients showed disorientation, agitation and/or somnolence as symptoms of hyponatremia. In the third case, no distinct symptoms related to hyponatremia was observed. None of these patients required invasive measures such as mechanical ventilation, hemodialysis or hemofiltration owing to hyponatriemia, and in none of them did the side effect result in a prolongation of hospital stay.

SE was finally successfully treated in 11 (79%) of the patients. Median mRS at discharge was 5. Three of the 13 patients died during their hospital stay, two of them owing to their severe acute illness that had caused the SE, the other one owing to a severe illness independent of etiology or treatment of SE.

4. Discussion

OXC was administered in patients with refractory SE of various etiologies and clinical presentations. In more than half of them, OXC was the last drug administered before SE cessation. Hyponatriemia was the only relevant side effect observed.

If success rate is defined as the proportion of SE patients in whom seizure activity stops after administration of an anticonvulsant drug regardless of the latency between first administration and cessation of epileptic activity, then the success rate of OXC in this cohort (57%) can be considered as high. In the same patient population, success rate for the third or later treatment step (including all substances applied) was mainly below 40%.[7] Intravenous lacosamide did not have a higher median success rate when looking across all case reports and studies, and including a relevant number of patients in whom lacosamide was used as first- or second-line therapy.[10] Topiramate had a higher success rate of 67% in a large swiss series of patients treated for refractory SE in an neurointensive care unit.[1] In a series from Pittsburgh[4] and in another swiss series,[11] success rate was only about 40%. Swisher and co-workers reported a success rate of 52% for pregabalin.[2] However, they included patients with acute repetitive seizures as well as patients with post-hypoxic SE, and pregabaline was initiated as second to fourth agent. Therefore, comparison is difficult. In another series with patients more similar to our patients,[3] pregabalin showed a success rate of slightly less than 50%. Differences between series are most likely owing to different etiologies, different doses and titration speed of the substances in question as well as of the concomitant therapies. Therefore, comparison of success rates across series and substances is hardly possible.

The majority of our patients were treated for nonconvulsive SE (as opposed to generalized convulsive SE). In adults, this is the most frequent SE form.[12] In our hospital cohort[7] that had similar distribution of age, etiology and semiology, nonconvulsive semiology was the only significant risk factor associated with refractoriness. This supports the potential effectiveness of OXC in SE.

In only 2 patients, response to OXC was seen within a short time frame (<6 h). In the other patients, response was delayed. Therefore it is possible that SE could have stopped anyway in those patients independent of the administration of OXC. However, enteral administration of anticonvulsants in critically ill patients results in very different and delayed resorption speed, owing to changes of gastrointestinal motility and perfusion. Thus, effective serum (and brain) levels of OXC may have been reached only with delay of days.

Maximum 10-OH-metabolite level of OXC was relatively low in some of the patients treated successfully. However, serum level was not routinely determined at peak or trough level, but could also come from a later phase days after first administration. Therefore, peak serum level (expected 3–5 h after enteral administration[5]) may have been much higher.

Three of 11 patients suffered from relevant hyponatriemia after OXC administration. This relatively high rate may be explained by the high prevalence of other risk factors for hyponatriemia in these patients such as co-administration of diuretics or insufficiency of the neurohormonal axis or both. In addition, our patients were relatively old which magnifies the hyponatremia risk.[13] Although none of the 3 patients required additional invasive treatment

Table 1
Patient characteristics.

Age, gender	Etiology	mRS at adm	Awareness at adm	AED before adm	Semiology	Latency SE onset → treatment onset	Course of treatment before OXC (Substance bolus in mg)	Latency SE-onset to OXC	OXC Dose (bolus → max. in mg)	Maximal 10-OH-metabolite serum level	OXC last drug (latency to SE cessation)	Adverse event related to OXC	SE finally stopped by ...	mRS at disch
77, m	Remote ischemia	3	Coma	VPA	LOC only	336 h	LZP 2 → LEV 3000 → PHT 1500 → VPA 2400	404 h	600 → 1200	n/a	No	none	n/a	5
74, f	Acute CNS inflammation	0	Confusion	LEV	Dyscognitive	0.5 h	CLZP 0.5 → LZP 6 → LEV 3000 → LCM 400	139 h	600 → 1200	n/a	Yes → 51 h	Hypo-natriemia	OXC	0
71, m	Acute hemorrhage	4	Coma	None	Dyscognitive	9 h	LZP 6 → LEV 3000 → PHT 1500 → LCM 400 → PROP	81 h	1800 → 1800	n/a	No	None	PHB	5
80, f	Remote ischemia	5	Coma	None	Simple motor	4 h	LZP 3 → PHT 1500 → LEV 3000 → LCM 400	67 h	900 → 1800	n/a	Yes (n/a)	None	n/a	5
77, f	Remote ischemia	3	Coma	LCM + Benzo	LOC only	1 h	LZP 2 → LEV 300 → LCM 400 → VPA 1200	213 h	600 → 1800	40 mg/l	Yes → 168 h	None	OXC	6
60, m	Acute CNS inflammation	3	Somnolence	None	LOC only	0.5 h	LZP 2 → LEV 3000 → PHT 1500 → LCM 400 → VPA 1800	50 h	600 → 1800	15.5 mg/l	Yes → 180 h	None	OXC	4
83, m	Remote ischemia	3	Coma	None	Generalized convuls.	0.5 h	LZP 2 → PHT 1500 → VPA 1800	96 h	600 → 1200	37.1 mg/l	Yes → 144 h	None	OXC	5
82, f	Remote ischemia	4	Sopor	None	LOC only	0.3 h	LZP 6 → LEV 3000 → LCM 400 → PHT 1500 → VPA 2400	34.5 h	600 → 1200	11.1 mg/l	Yes → 122.5 h	None	OXC	4
86, f	Tumor and remote trauma	3	Sopor	LEV	Simple motor	1.75 h	LZP 4 → LEV 2000 → LCM 400	621 h	600 → 1200	30.7 mg/l	No	None	PHT	6
80, f	Remote ischemia	4	Awake	GBP	Dyscognitive	19.25 h	LZP 1	22 h	600 → 1800	n/a	Yes → 3 h	None	OXC	4
84, f	Remote ischemia	4	Somnolence	None	Simple motor	1.2 h	LZP → 2 LEV 2000	49.5 h	600 → 1200	n/a	Yes → 4 h	None	OXC	4
79, m	Acute encephalitis	0	Somnolence	None	LOC only	26 h	LZP 2 → LEV 3000 → LCM 400 → VPA 3000 → PROP → TOP 800	262 h	1200 → 2400	31.4 mg/l	No	Hypo-natriemia	n/a	6
56, f	Acute trauma	3	Somnolence	LEV	Generalized convuls.	0.3 h	MDZ 5 → LEV 3000 → LCM 400 → VPA 2000	67 h	600 → 1800	11.7 mg/l	Yes → 151 h	Hypo-natriemia	OXC	3

adm, admission; disch, discharge; n/a, not applicable; SE, status epilepticus; f, female; m, male; LOC, loss of consciousness; OXC, oxcarbazepine; benzo, benzodiazepine; LCM, lacosamide; LZP, lorazepam; MDZ, midazolam; LEV, levetiracetam; GBP, Gabapentin; PHT, phenytoin; VPA, valproate; PROP, propofol; TOP, topiramate; mRS, modified Rankin scale.

owing to this adverse reaction, patients with SE treated with OXC need to be monitored carefully for hyponatriemia.

There are several limitations to this study. First, patient numbers are rather small. In addition, this is a monocentric series. Therefore, the results cannot be easily generalized to other circumstances. We defined 'successful treatment' as OXC being the last substance added before cessation of SE. This is a quite inclusive definition in contrast to more conservative definitions used in studies regarding intravenously applied substances and may overestimate the effect of OXC. However, OXC can only be applied enterally, and is a prodrug of the effective metabolite. Therefore, less strict criteria may be more adequate for this substance. Finally, this is a retrospective analysis with all inherent problems. However, in our center, a standardized SE treatment documentation is established which helps overcome the usual diversity of documentation quality.

Literally every report regarding treatment of refractory SE ends with the call for a large prospective and randomized trial. Until such data are available, this small dataset could help the treating physician when choosing between therapy options in this hard-to-treat patient group.

5. Conclusion

Oxcarbazepin was the last drug before cessation of refractory SE in more than half of the patients and thus may be an effective treatment option. However, patients need to be monitored closely for hyponatremia.

Conflicts of interest

Dr. Kellinghaus received honoraria and travel support from UCB, Eisai, Pfizer, Desitin, and NRSIGN. He has served on advisory boards for UCB and Eisai. Dr. Stögbauer received honoraria and travel support from Bayer, Biogen TAD, Novartis, Biogen, Merck Serono, Pfizer, TEVA and Sanofi-Aventis. Dr. Berning has no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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